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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,421	02/19/2002	Manabu Wada	HAYAK-9	9291

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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,421	WADA ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27 and 35-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27 and 35-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection on 20 January, 2006. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Claims 27 and 35-46 are pending and currently under examination in the instant application.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 27, 35, 36, 41, and 42 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q.

90 (C.C.P.A. 1976). Perusal of the disclosure, including the originally filed claims, failed to provide support for the claim limitation wherein the ATF "does not extend beyond amino acid 178 of the sc-uPA". The disclosure unambiguously describes the processing of PrePro-uPA/sc-uPA to Pro-uPA to HMW-uPA to LMW-uPA. The Pro-uPA precursor is cleaved between aa 178 and 179 to produce HMW-uPA. HMW-uPA consists of an A chain (aa 21-178) and a B chain (aa 179-431). The ATF is produced by cleavage of the HMW-uPA to produce the LMW-uPA form. During this process, an amino terminal fragment (ATF: aa 21-155) is produced. The focus of the invention clearly appears to be on this fragment (i.e., see pages 5, 9, and 10). The inventors do not appear to contemplate making and using just the A chain from HMW-uPA (aa 21-178) or fragments thereof. The specification does not disclose the isolation, purification, or use of any of these fragments (i.e., aa 21-158, 21-163, 21-167, 21-174, etc.). Therefore, the skilled artisan would reasonably conclude that applicants were not in possession of the claimed invention at the time of filing. Applicants may obviate the rejection by directing the claim language toward the ATF (aa 21-155).

Enablement

Claims 35-46 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward methods for the treatment of HIV-1 infection in patients through the administration of ATF or sc-uPA fragments comprising this region. The legal considerations that govern

enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The state-of-the-art vis-a-vis HIV-1 antiviral development is best characterized as one of unpredictability. There are several problems that have contributed to the unpredictability in the field including the failure of many *in vitro* tissue culture assays to actually predict clinical efficacy. Another problem is that *in vivo* animal models often fail to show structural/functional relatedness between the two systems (i.e., concerning macaques and humans, does the antiviral act on a target that is conserved in both HIV and SIV) and significant reductions in viral load (preferably several orders of magnitude). Problems with HIV antivirals in the clinic have included short serum half-lives, poor bioavailability, rapid clearance rates, sequestration of the antiviral by serum proteins, viral drug resistance, uneven drug distribution throughout the body, and the failure to achieve adequate

intracellular concentrations due to drug efflux from the cell, etc. (Yarchoan *et al.*, 1993; Gait and Karn, 1995; Patience et al., 1994; Back, 1999). These pharmacological problems are unpredictable and are not adequately addressed by *in vitro* tissue culture assays.

2) The disclosure fails to provide any working embodiments. The disclosure asserts that a novel antiviral activity has been attributed to ATF. The specification provides simple *in vitro* tissue culture assays wherein it is concluded that this compound will prove to be a useful pharmaceutical for the treatment of HIV-1 infection. Considering the unpredictability of the prior art as it pertains to HIV-1 antiviral development, the skilled artisan would readily question the ability of this compound to effectively combat HIV-1 infection in the clinic. Particularly when the skilled artisan considers the large amount of virus produced on a daily basis (~10^{10} virions/day). More meaningful indices of the effectiveness of any given putative antiviral are the ability of the compound to produce significant reductions in viral load accompanied with a meaningful clinical response. The disclosure clearly fails to provide such information.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the

> subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 27 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Stoppelli *et al.* (1985) in view of Imamura *et al.* (1999). The claims are directed toward a composition comprising an amino terminal fragment of HMW-uPA in a sterile aqueous or non-aqueous medium wherein said fragment comprises the ATF (aa 21-155) and does not extend beyond aa 178 of the sc-uPA. Stoppelli and colleagues provide isolated and purified ATF (residues 1-135 or 21-155 according to applicants' numbering scheme). Thus, the produce is well-known and widely available. This teaching does not disclose the preparation of a composition comprising ATF in a "sterile aqueous or non-aqueous medium". However, Imamura and colleagues provide pharmaceutical compositions comprising polypeptides. The preparation of pharmaceutical compositions is well-known in the art. Imamura and colleagues clearly state that various pharmaceutically

acceptable solvents, fillers, carriers, and auxiliary agents can be used and these composition may be in the form of a liquid, lotion, aerosol, powder, tablet, capsule, suppository, etc. (see col. 5, lines 19-38). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare pharmaceutical compositions, as taught by Imamura *et al.* (1999), comprising the biologically active ATF polypeptide provided by Stoppelli *et al.* (1985), since this would provide a useful composition for a number of different biochemical, immunological, and pharmacological applications.

Claims 27 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Li *et al.* (2003). The claims are directed toward a composition comprising an amino terminal fragment of HMW-uPA in a sterile aqueous or non-aqueous medium wherein said fragment comprises the ATF (aa 21-155) and does not extend beyond aa 178 of the sc-uPA. Li and colleagues disclose the preparation of defective adenoviral vectors encoding the ATF that are useful for the treatment of tumors by inhibiting growth or metastases. This teaching does not provide a composition comprising the ATF alone in a pharmaceutical composition. However, the preparation of pharmaceutical compositions is well-known in the art as evidence by the details set forth in col. 18 of this teaching. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare pharmaceutical compositions comprising the ATF polypeptide provided by Li *et al.* (2003), since this would provide a useful composition for a number of

different biochemical, immunological, and pharmacological applications.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, James C. Housel, can be reached at (571) 272-0902. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on

access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

31 March, 2006